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Reply to M. Lambertini et al

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CORRESPONDENCE

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Lambertini et al[1] challenge the conclusion of the randomized controlled study by Demeestere et al,[2] which showed lack of gonadal protective effect from gonadotropin-releasing hormone agonist (GnRHa) suppression in women with lymphoma based on quantifiable serum ovarian reserve markers. Lambertini et al[1] suggest that their studies[3,4] have provided consistent results and support conclusions opposite of those of Demeestere et al.[2] However, the studies differ significantly in their design, primary outcome measures, patient populations, and pregnancy outcomes (Table 1).[5-7]

Lambertini et al[1] cite their own meta-analysis as proof of GnRHa's effectiveness for fertility preservation. As previously discussed,[5] meta-analyses do not correct for original study weaknesses, and there is no biologic rationale in limiting meta-analyses to breast cancer. When all studies that also include hematologic cancers are meta-analyzed, there remains no benefit from GnRHa.[8]

In addition to using a specific definition of premature ovarian failure (POF) and primary ovarian insufficiency (POI) involving amenorrhea and follicle-stimulating hormone greater than 40 mIU/mL as the primary outcome measure, Demeestere et al[2] measured serum anti-müllerian hormone (AMH) levels to corroborate their findings. Serum AMH is the most reliable quantitative marker in measuring ovarian reserve, diagnosing occult POI (a state that is induced in most women by breast cancer chemotherapy), and predicting age at menopause. None of the studies that used AMH as a marker showed benefit from the addition of GnRHa treatment (Table 1).

Lambertini et al[1] surmise that pregnancies nullify the designation of the study patients as having POI/POF. This is not a correct assessment. First, there is 5% to 15% spontaneous live birth rate among those who are designated to be in POI. Second, spontaneous pregnancies do occur, even among those who are induced to become menopausal by highly gonadotoxic preconditioning chemotherapy for hematopoietic stem-cell transplantation. Because in these young patients the egg quality is not reduced after chemotherapy, the conceptions may be a result of the ability of few remaining follicles to ovulate sporadically or possibly the ability of some oocytes to self-repair chemotherapy-induced DNA damage.[5,9] Hence, pregnancy and POF/POI are not exclusive; what is important is that the probability of pregnancy is significantly reduced after gonadotoxic chemotherapy.

Because breast cancer chemotherapy regimens often do not induce complete POF/POI but rather result in occult POI, many women still retain some reserve and have the ability to spontaneously conceive, albeit at reduced probability. Hence, it is not surprising that, in an unblinded and non–placebo-controlled design where the data are not corrected for pregnancy intent and attempt and the women who are aware of their GnRHa treatment could be more motivated to attempt pregnancy, one may inaccurately interpret those incidental conceptions as being GnRHa-treatment enabled.

Lambertini et al[1] also suggest that the use of norethisterone by Demeestere et al[2] blunted GnRHa's benefit on ovarian function by suppressing the pituitary gonadotropin secretion in the control group. This claim has numerous weaknesses. First, primordial follicles that make up the ovarian reserve are quiescent, do not express gonadotropin or GnRHa receptors,[5] and hence have no pathway for responding to changes in serum gonadotropin on gonadotropin-releasing hormone levels. Second, if the authors' claim were to be true, we would then expect any form of ovarian suppression including oral contraceptives to preserve ovarian function against chemotherapy, which is not the case. Third, unlike combined contraceptive pills, progestin-only treatments have a weak suppressive effect on serum gonadotropin levels. They induce amenorrhea primarily by their effects on endometrium, not the pituitary. Fourth, to further cast doubt that GnRHas preserve ovarian function by suppressing serum follicle-stimulating hormone levels, a time-honored randomized study by Waxman et al[10] showed that serum gonadotropin levels are not suppressed below minimum physiologic levels seen during a menstrual cycle (excluding the time of ovulation) even after months of administration. Finally, Lambertini et al[1] suggest that GnRHas may preserve ovarian endocrine function even if they do not improve the chance of pregnancy. This hypothesis does not par with ovarian biology. Hormone production and fertility are coupled functions of the ovary. Hence, in studies that show continued vaginal bleeding but not preservation of fertility,[3,4] one will have to look at explanations other than the effectiveness of GnRHa treatment. These include observational biases as a result of lack of blinding and placebo and use of nonquantitative and subjective markers such as the return of any kind of menstrual bleeding.[5-7,11]

On the basis of reliable data and basic ovarian biologic facts, GnRHa suppression cannot be considered as an effective method of ovarian or fertility preservation. Just-in-case administration of GnRHas over prolonged periods of time cannot be justified given the cost, potential adverse effects including irreversible bone loss, and the risk of counseling away from proven methods of fertility preservation via embryo, oocyte, and ovarian tissue cryopreservation.[11]

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Table 1. Comparison of Randomized Studies That Used Serum AMH to Studies by Lambertini et al[3] and Moore et al[4]

Study	Cancer Type	Patient Age (years)	Sample Size	Primary Outcome	Secondary Outcome	Conclusion	Limitations
Demeestre et al,[8a] 2013	Hodgkin and non-Hodgkin lymphoma	18-38	GnRHa plus Chemo plus norethisterone acetate, n = 65; Chemo plus norethisterone, n = 64	POF (FSH level > 40 mIU/mL) at 12 months of follow-up	AMH; early menstrual FSH and E2	Triptorelin was not associated with a significantly decreased risk of POF	Relatively short follow-up period
Demeestre et al,[2] 2016	Hodgkin and non-Hodgkin lymphoma	18-38	GnRHa plus Chemo, n = 32; Chemo alone, n = 35	POF (FSH level > 40 mIU/mL) at approximately 66 months of follow-up	AMH; early menstrual FSH and E2; pregnancy rate	Triptorelin was not associated with a significantly decreased risk of POF and did not influence future pregnancy rate	One of the best-designed studies
Elgindy et al,[8] 2013	Breast cancer (ER negative)	18-40	Early Chemo alone, n = 25; early Chemo and antagonist and agonist, n = 25; delayed Chemo alone, n = 25; delayed Chemo plus GnRHa, n = 25	Resumption of menses 12 months after Chemo	Resumption of regular menses; random FSH, LH, and E2, as well as AFC and AMH, 12 months after the end of Chemo	Triptorelin cotreatment does not offer a significant protective effect on ovarian function	One of the best-designed studies
Gerber B (ZORO study),[8b] 2011	Breast cancer (ER negative)	18-45	Chemo plus goserelin, n = 30; Chemo alone, n = 31	Resumption of menses (2 consecutive menstrual periods within 21-35 days in a time frame of 6 months after Chemo) after 24-month follow-up	Time until recovery of regular menses; random AFC, AMH, FSH, LH, and E2 at 6, 12, 18, and 24 months after end of Chemo; pregnancy rate	Patients using goserelin along with Chemo did not experience a statistically significantly lower risk of amenorrhea 6 months after Chemo compared with patients receiving Chemo alone	Serum FSH and E2 were not drawn on cycle day 2 or 3, but a less cycle day–dependent marker, AMH, was used
Moore et al,[4] 2015	Breast cancer (ER negative)	18-49	Chemo alone, n = 69; Chemo plus goserelin, n = 66	Rate of POF (ovarian failure was defined as amenorrhea for the preceding 6 months and FSH levels in the postmenopausal range at 2 years)	Pregnancy within the past 5 years, assessed annually; ovarian dysfunction (amenorrhea in the preceding 3 months) and FSH, E2, or inhibin B levels in the postmenopausal range	Administration of goserelin with Chemo appeared to protect against ovarian failure	Trial was terminated prematurely as a result of lack of funding; any bleeding without regularity was considered as menstruation; random hormone profile measurements without using AMH; pregnancy rates are not different when intent is considered
Lambertini et al,[3] 2015)	Breast cancer (ER negative and positive)	24-45	Chemo alone, n = 133; GnRHa plus Chemo, n = 148	Early menopause, resumption of menses (evaluated by yearly assessment of menstrual activity)	Long-term ovarian function (considered as preserved by the occurrence of at least 1 menstrual cycle), pregnancies, and disease-free survival	Triptorelin was associated with higher long-term probability of ovarian function recovery, without a statistically significant difference in pregnancy rates	Any bleeding without regularity was considered as menstruation; no information regarding the definition of postmenopausal status; no difference was found in terms of pregnancy outcomes among groups

Abbreviations: AFC, antral follicle count; AMH, anti-müllerian hormone; Chemo, chemotherapy; E2, estradiol; ER, estrogen receptor; FSH, follicle-stimulating hormone; GnRHa, gonadotropin-releasing hormone agonist; LH, luteinizing hormone; POF, premature ovarian failure; ZORO, Zoladex Rescue of Ovarian Function.

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